The endocannabinoid system

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The endocannabinoid system: Overview of an emerging multi-faceted therapeutic target☆

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ABSTRACT

The endocannabinoids anandamide (AEA) and 2-arachidonoylglyerol (2-AG) are endogenous lipid mediators that exert protective roles in pathophysiological conditions, including cardiovascular diseases. In this brief review, we provide a conceptual framework linking endocannabinoid signaling to the control of the cellular and molecular hallmarks, and categorize the key components of endocannabinoid signaling that may serve as targets for novel therapeutics. The emerging picture not only reinforces endocannabinoids as potent regulators of cellular metabolism but also reveals that endocannabinoid signaling is mechanistically more complex and diverse than originally thought.

1. Introduction

In ancient times, the depression-pain comorbidity was treated through the use of extracts of the *Cannabis sativa* plant, commonly known today as marijuana. Humans and animals alike naturally synthesize endogenous cannabinoids, chemical compounds that activate the same receptors as Δ^9-tetrahydrocannabinol (Δ^9-THC), the active component of marijuana. Use of marijuana for addressing pain due to various reasons has become a topic of concern in terms of possible addiction, drug abuse as well as regulatory issues. Although historically, the use of marijuana dates back to over 2000 BCE, the biological action of Δ^9-THC remained elusive until recently. The biological receptor of Δ^9-THC on the cell surface has been previously identified and described [1,2]. Characterization of this receptor led to understanding of the mode of action of Δ^9-THC that underlies its wide spectrum of pharmacological effects, which encompass euphoria, calmness, appetite stimulation, sensory alterations and analgesia [1,2].

Identification in the late 1980s of the first endogenous cannabinoid-like substance, anandamide (AEA), in pig brain reiterated the significance of the so-called cannabinoid receptor and its endogenous ligands in the control of a wide variety of biological activities [1,2]. The name 'anandamide', derived from Sanskrit ('ananda' meaning bliss) is given to *N*-arachidonoylethanolamine, for its cannabinomimetic effects. Subsequently, another endogenous cannabinoid compound known as 2-arachidonoylglycerol (2-AG) was identified [3,4]. Of note, the two endocannabinoids were derivatives of arachidonic acid. Considering that these compounds are endogenous and cannabinomimetic, acting on the cannabinoid receptors, they were termed as endocannabinoids (ECs).

In this article we present a brief overview of the endocannabinoid system, including the physiological and pathophysiological roles of the endocannabinoid receptors, and discuss the application of ECs as potent regulators of cellular metabolism.

2. The endocannabinoid system at a glance

Although the first EC to be identified was AEA, 2-AG is the most abundant in the brain [5]. Over the past few decades several endogenous fatty acid amides and monoacylglycerols have been discovered and extensively studied, providing with a compelling evidence that these compounds serve as a new and additional class of endogenous signaling molecules involved in a plethora of physiological function. These molecules, and their physiological function and significance, has been extensively documented and discussed in details by Ezzili et al. [6,7]. Multiple human and animal studies support that endocannabinoids play a key role in memory, mood, brain reward

Abbreviations: THC, Tetrahydrocannabinol; EC, Endocannabinoid; CB1R, Cannabinoid receptor type 1; CB2R, Cannabinoid receptor type 2; AEA, Arachidonoylethanolamine; 2-AG, 2-Arachidonoylglycerol; FAAH, Fatty acid amide hydrolase; MGL, Monoacylglycerol lipase

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systems, drug addiction, and metabolic processes, such as lipolysis, glucose metabolism, and energy balance [6].

Several competing pathways for AEA biosynthesis have been described. AEA biosynthesis is initiated following a postsynaptic neuronal depolarization and an influx of calcium. The calcium then activates.N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) and diacylglycerol (DAG) lipase, each of which forms AEA and 2-AG, respectively [5,7]. The anterograde neurotransmitter transmission and retrograde EC modulation form the closed signaling loop.

The biological effects of endocannabinoids are mediated by two members of the G-protein coupled receptor (GPCR) family, cannabinoid receptors 1 (CB1R) and 2 (CB2R). The CB1R is the prominent subtype in the central nervous system (CNS) and has drawn great attention as a potential therapeutic avenue in several pathological conditions, including neuropsychological disorders and neurodegenerative diseases. Furthermore, endocannabinoids also modulate signal transduction pathways and exert profound effects at various peripheral tissues. Although cannabinoids have therapeutic potential, at present, their psychoactive effects have largely limited their use in clinical practice.

Owing to the lipophilic nature of endocannabinoids, it was initially thought that these compounds exert various biological effects by disrupting the cell membrane nonspecifically. However, following the discovery of THC and subsequent emerging of several chemically synthesized cannabinoids, the successful mapping and the pharmacological characterization of cannabinoid binding sites in the brain revealed the existence of a putative CBR and its similarity to GPCR nature, which was matched with the properties of an orphan GPCR, now known as CB1R.

3. Tissue distribution of cannabinoid receptors

Recently, the differential expression pattern of CB1R has been characterized at the mRNA level in human brain, skeletal muscle, liver, heart and pancreatic islet [8,9] The full-length CB1R dominates in the brain and skeletal muscle, whereas the CB1Rb (having a 33 amino acid deletion at the *N*-terminus) shows a higher expression level in the liver and pancreatic islet cells where it is involved in metabolic regulation [8,9].

CB1R is particularly concentrated on both γ-aminobutyric acid (GABA)–releasing neurons (inhibitory neurons) and glutamatergic-releasing neurons (excitatory). Hence, activation of CB1R leads to retrograde suppression of neurotransmitter release, which may be excitatory or inhibitory depending on the location in the brain [10–12]. Interestingly,.Cb1r.gene polymorphisms have been described but their functional effects are not well-characterized. Some polymorphisms are associated with anxiety and depression. Additionally, CB1R is also expressed in some non-neuronal cells, including immune cells [13].

The central distribution pattern of CB1R is heterogeneous and accounts for several prominent pharmacological properties of CB1R agonists, for example their ability to impair cognition and memory and to alter the control of motor function. Thus the cerebral cortex, hippocampus, lateral caudate putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and the molecular layer of the cerebellum all are populated with particularly high concentrations of CB1R [14,15]. In line with the analgesic properties of cannabinoid receptor agonists, CB1R is also found on pain pathways in the brain and spinal cord and at the peripheral terminals of primary sensory neurons [16,17]. Although the concentration of CB1R is considerably less in peripheral tissues than in the central nervous system, this does not mean that peripheral CB1R are unimportant. Thus in some peripheral tissues, discrete regions such as nerve terminals that form only a small part of the total tissue mass are known to be densely populated with CB1R. Peripheral tissues in which CB1R is expressed on neurons include the heart, vas deferens, urinary bladder and small intestine [15,18,19].

CB2R is encoded by the gene *Cnr2*, and shares only 44% sequence homology with CB1R at the protein level. The CB2R exhibits greater species differences among humans and rodents in comparison to CB1R, as the amino acid sequence homology is ~80% between humans and rodents [20,21]. CB2R is located peripherally, with a high density on immune-modulating cells, including microglia in the brain, the function of this receptor including modulation of cytokine release and of immune cell migration. In humans, two isoforms of the CB2R have been identified, with one predominantly expressed in testis and at lower levels in brain reward regions, whereas the other is mainly expressed in the spleen and at lower levels in the brain [21]. The testis isoform has a promoter that is 45 kb upstream from the spleen isoform [21]. Thus far, four rat CB2R isoforms and two mouse isoforms have been discovered [20,21].

4. Endocannabinoid signaling:.physiological and pathophysiological.roles

4.1. Chronic stress

Although stress responses can be life-saving in the face of a threat, chronic stress often has negative health effects. The EC system is the central mediator of the stress response. The EC system regulates the release of stress-induced neurotransmitters including the systemic release of norepinephrine and cortisol, and thus plays a role in the stress alterations of mood, cognition, and activation of the hypothalamic-pituitary-adrenal axis [23]. The EC system may also mediate some of the metabolic effects that glucocorticoids exhibit on lipid metabolism, leading to hepatic steatosis and potentially contributing to the metabolic syndrome [24]. Therefore, the EC system is an important control point and therapeutic target to reduce the deleterious effects of chronic stress [25].

4.2. Obesity

CB1R is important for energy balance in the body [26]. With fasting or starvation, AEA and 2-AG levels increase in the limbic forebrain and, to a less significant extent, in the hypothalamus. CB1R activation increases food intake and effects whole-body energy metabolism through coordination of the mesolimbic reward system and the hypothalamus' appetite control pathway [12,26]. This receptor also promotes food intake by increasing odor detection via stronger odor processing in the olfactory bulb [27]. Some obese individuals may have excess CB1R activation. Obese and overweight individuals may have a mutation in fatty acid amide hydrolase (FAAH), the enzyme that degrades AEA. This can lead to increased levels of AEA (~15-fold increase in FAAH null mice) and stimulation of the hypothalamic appetite control center [26].

It is uncertain if there is a regulatory feedback loop between the EC system and obesity. Wild-type mice that develop diet-induced obesity have a hyperactive EC system, with an increase in receptor availability and an increase in circulating ECs. In pre-satiated mice, an intra-hypothalamic injection of AEA induced substantial hyperphagia. Inactivation of CB1-R receptors decreases plasma insulin and leptin levels, ultimately leading to a more efficient energy metabolism [27,28].

4.3. Nervous system

The EC system obviously plays a significant role in the normal functioning of the brain, spinal cord, and peripheral nervous system. Therefore, the EC system can either cause or become altered by diseases of the neurologic system. For example, hyperactivity of the EC system reduces dopaminergic tone in the basal ganglia, contributing to the pathophysiology of Parkinson disease [29]. Other diseases with potentially significant EC system interactions include multiple sclerosis, seizure disorders, Alzheimer's disease, Huntington disease, amyotrophic lateral sclerosis, and psychiatric diseases such as schizophrenia [30,31]. CB2Rs may have some relationship to depression based on animal

studies and the finding of a high-incidence of *Cb2r* polymorphisms in a depressed Japanese population [13].

4.4. Pain

Pain is already a well-established and important therapeutic application for ECs. CB1R agonists act on nociceptive interneurons in the dorsal horn of the spinal cord to alleviate pain. In addition, CB2R-selective agonists have proven to be helpful in reducing inflammation and undoing established inflammation hypersensitivity involved in peripheral pain and skin disorders [22,32]. It is believed the CB2Rs may have a protective effect on inflammation and autoimmunity [13,22].

4.5. Heart and blood vessels

CB1R activation aids in vasodilation and cardiac contractility, regulating blood pressure and improving left-sided heart function. CB2R has been implicated in the inflammation in atherosclerotic plaques. In this regard, CB2R activation is a therapeutic strategy for reducing atherosclerotic plaque inflammation and reducing vulnerability to rupture and thrombosis [33]. Previously, several studies have linked impaired glucose uptake and insulin resistance (IR) to functional impairment of the heart. Additionally, endocannabinoids have also been implicated in cardiovascular disease. However, the mechanisms involving endocannabinoid signaling, glucose uptake, and IR in cardiomyocytes were understudied..Addressing this gap in knowledge, recently, we have demonstrated that CB1R activation stimulates the energy-sensing AMP-activated protein kinase (AMPK) to inhibit inflammation and subsequently ameliorate cardiomyocyte insulin resistance [34]. In fact, beneficial effects of AMPK activation in the heart and vessel wall are widely known [35,36] suggesting that a greater part of the established EC effects in the cardiovascular system are mediated by downstream AMPK activation. Therefore, this recent finding provides an important basis towards the understanding and furthering of the concept that CB1R can be considered as a potential therapeutic alternative in cardiac diseases such as ischemia-reperfusion injury or myocarditis [37], where immediate energy flux to the tissue is of utmost importance (Fig. 1). Future investigations and clinical trials are warranted in this regard and will lead to a better understanding, utilization and application of cannabinoid signaling in a tissue-specific manner.

4.6. Cancer

Both marijuana and ECs are anti-inflammatory, anti-proliferative, anti-invasive, anti-metastatic, and pro-apoptotic in most cancers, both in vitro and in vivo, in animals. In some cancers, ECs are pro-proliferative and anti-apoptotic, but in the majority they show cell cycle arrest, autophagy, apoptosis, and tumor inhibition. At present, cannabinoid cancer therapy is limited to nausea and pain, but future studies are needed to determine its full chemotherapeutic potential [32,38–40].

4.7. Gastrointestinal system

Activation of CB1R and, to a lesser extent, CB2R, by AEA also reduces gastrointestinal motility and secretions. Activation of CB1R inhibits pro-inflammatory responses in the colon [41,42].

4.8. Liver

CB1R receptors aid in modulating hepatic metabolism, including gluconeogenesis [43], lipogenesis [44,45] and bile acid synthesis [46]. Activation of CB1R in the liver stimulates fatty acid synthesis, causing hepatic steatosis and diet-induced.obesity [44]. In addition, CB1R promotes hepatic fibrosis and contributes to the hemodynamic abnormalities seen in cirrhosis. By reducing inflammatory cell infiltration and lipid peroxidation, CB2R activation is protective against hepatic ischemia–reperfusion injury. Targeting the hepatic EC system may have therapeutic potential in a variety of liver diseases (reviewed in ref. 26).

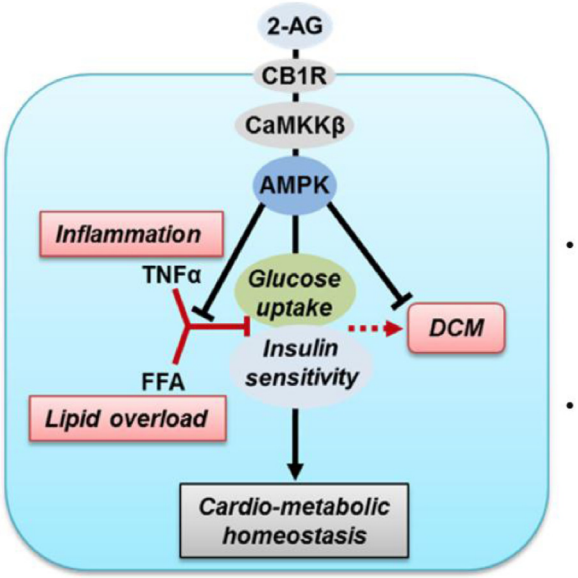

Fig. 1. Schematic presentation of the proposed therapeutic application of 2-AG in cardiovascular disease. 2-AG has a beneficial effect on the insulin signaling pathway in dysregulated cardio-metabolic conditions. In addition, 2-AG may also exert anti-inflammatory effects via activation of AMPK signaling pathway in cardiomyocytes. Abbreviations: AMPK, AMP-activated kinase; CaMKK, Ca^{2+}/calmodulin-dependent protein kinase; DCM, diabetic cardiomyopathy. Reproduced, with permission, from ref. 34.

4.9. Reproductive system

The EC system has a role in reproduction [47]. CB1R is found in the male (Leydig cells) and the female (ovary, ducts, uterus). Furthermore, normal folliculogenesis and spermatogenesis may require the EC system. CB1R is also present in the placenta and is necessary for embryo implantation [37]. The use of cannabis is associated with implantation failure, spontaneous miscarriage, fetal growth restriction, and premature birth in humans. Future research efforts will be needed to unravel the full complexity of the EC system involvement in the process of reproduction.

4.10. Skeletal system

In addition to immunomodulatory pathways, CB2R is involved in maintaining proper bone mass. CB2R is abundant in osteocytes, osteoclasts, and osteoblasts. CB2R agonists enhance endocortical osteoblast reproduction and activation, while inhibiting osteoclastogenesis [48]. Owing to the lack of detailed research, extensive future efforts will be needed to unravel the underlying significance of the EC system involvement in the process of osteogenesis.

Table 1 summarizes the potential avenues of therapeutic intervention by targeting/utilizing the endocannabinoid system.

5. Endocannabinoid degradation

Endocannabinoids have a short life span. AEA and 2-AG are quickly degraded through transport protein-mediated reuptake and hydrolyzation by either FAAH or MAG lipase, respectively [5,7]. Degradation may be an important regulatory control point, since inactivation of

Table 1
Potential therapeutic applications for cannabinoid pharmacologic intervention.

- Pain
- Anti-nausea
- Glaucoma
- Cachexia
- Neurologic diseases: Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, alcohol-induced neuro-inflammation/ neurodegeneration, traumatic brain injury, stroke, seizures
- Autoimmune diseases: Autoimmune uveitis, systemic sclerosis, inflammatory bowel disease
- Infection: HIV-1 brain infection
- Psychiatric disorders: Anxiety-related disorders, impulsivity, bipolar disorder, personality disorders, attention-deficit/hyperactivity disorder, substance abuse and addictive disorders, anorexia nervosa
- Cardiovascular diseases: Atherosclerosis
- Gastrointestinal diseases: Gut motility disorders, inflammatory bowel syndrome, chronic liver diseases, alcoholic liver disease
- Diabetic nephropathy
- Osteoporosis
- Cancer: Breast, prostate, skin, pancreatic, colon, and lymphatic, among others

FAAH results in 15-fold elevated AEA levels in genetic FAAH knock-out mouse brains. Furthermore, these enzymes, FAAH and MGL, have become therapeutic targets for pharmacologic interventions of the EC system. FAAH inhibition has shown the advantages of a lack of abuse potential or physical dependence compared with MGL [7,13].

Regrettably, however, in early 2016, the exceptional occurrence of serious adverse events (SAEs) in a phase I clinical trial conducted by the Biotrial Pharmacology Center (Rennes, France) on behalf of Bial-Portela & Ca. SA (São Mamede do Coronado, Portugal) came into limelight. The trial involved the compound BIA 10-2474, a drug designed to inhibit FAAH. The most serious symptoms had central neurological features, the worst being those associated with a single case of coma which rapidly lead to brain death. Of the other 5 hospitalized participants, 2 had serious neurological damage (with clinical improvement apparently occurring within a few days). Because of these events, the trial was immediately suspended [49]. Other less important enzymatic pathways exist, demonstrating redundancy in EC degradation. Interestingly, the catabolite arachidonic acid is a precursor for the cyclooxygenase (COX)–2 enzyme, leading to a number of bioactive eicosanoids (e.g., prostaglandins, prostacyclin, thromboxane, leukotrienes). The significance of the EC–COX-2 eicosanoid pathway is under investigation [50,51].

6. Pharmacologic therapy

6.1. Cannabinoid receptor agonists

FAAH inhibitors/inactivators are continuously under investigation because of their ability to increase the concentration of endocannabinoids. Endocannabinoids are lipid mediators released on demand from membrane phospholipid precursors. Their targets are the CBRs, but other receptors can be involved in their action, such as GPR55, peroxisome proliferator-activated receptors (PPARs) and vanilloid receptors ($TRPV_1$). The endocannabinoid system has been implicated in a wide range of physiological processes such as those associated with chronic pain, metabolic disorders, psychoses, nausea and vomiting, depression, and anxiety disorders [reviewed in ref. 52–56]. Some exogenous cannabinoids acting on CBRs.are currently used in therapeutics (e.g., Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Cesamet®, Marinol®, Sativex®) involving a variety of indications such as anorexia, neuropathic pain and multiple sclerosis, depending on the country in which the drugs are marketed (Table 2). However, such treatments may have neurological side effects (including impairment of cognition and motor functions and a predisposition to psychoses), notably when these agents are used for long-term treatment [57,58].

THC and cannabidiol (which together make up the drug Sativex^R) are active components of.Cannabis sativa that bind to CB1R and CB2R. Their bioavailability is unknown. A buccal spray is approved for use for neuropathic pain associated with multiple sclerosis in Canada only [59–61].

Dronabinol.(Marinol^R), a synthetic THC, is a CB1R and CB2R agonist that has been approved by the US Food and Drug Administration (FDA) for use as an antiemetic for chemotherapy and an appetite stimulant for persons with acquired immunodeficiency syndrome (AIDS). Its bioavailability is 10% [61]. Significant adverse effects have been reported particularly central nervous system toxicity [62].

Nabilone.(Cesamet^R) is a synthetic analogue of THC; it is a CB1R and CB2R agonist that has been FDA approved as an anti-emetic in chemotherapy patients in whom all other therapy has failed. Unapproved use is employed in patients with upper motor neuron syndrome who have spasticity-related pain not controlled by conventional treatment [63].

6.2. CB1 receptor antagonists

CB1Rs activate the dopaminergic reward system. Commonly abused drugs, such as nicotine, opiates, THC, and alcohol, share a common pathway, the dopaminergic surge in the *nucleus accumbens*. Independent studies involving humans and mice, respectively, reported an increase in smoking cessation rates, decreased alcohol intake, and a reduction in cocaine-seeking behavior with CB1-R antagonism. Rimonabant (Acomplia^R or Zimulti^R) is a selective CB1R antagonist, SR141716, with an affinity to centrally acting CB1R. Rimonabant was sold in Europe for the treatment of obesity. It was not approved in the United States and later withdrawn because of psychiatric effects, especially depression [64–67]. Nevertheless, the EC system is a ubiquitous regulator of cellular function in both health and diseases, which offers many potential therapeutic targets. Table 2 provides a listing of EC system agonist and antagonist interventions with therapeutic potential [68].

6.3. CB2 receptor antagonists/ inverse agonists

The most notable CB2R-selective antagonists/inverse agonists are the Sanofi-Aventis diarylpyrazole, SR144528 [69] and 6-iodopravadoline (AM 630) [70]. Both compounds bind with much higher affinity to CB2R than to CB1R, exhibit marked potency as CB2R antagonists and behave as inverse agonists that can by themselves produce inverse cannabimimetic effects at CB2R [14,71]. For example, AM 630 has been reported to reverse CP 55,940-induced inhibition of forskolin-stimulated cyclic AMP production by human CB2R-transfected CHO cell preparations at concentrations in the nanomolar range (EC50 = 129 nM) and to enhance forskolin-stimulated cyclic AMP production by the same cell line when administered by itself (EC50 = 230 nM) [70], albeit with an efficacy that appears to be somewhat less than the inverse efficacy displayed by SR144528 in this bioassay [72]. At the CB1R, AM 630 has been found to behave in some investigations as a low potency partial agonist [70,73] but in others as a low potency inverse agonist [74,75].

7. Further investigation

Endocannabinoids are crucial to bioregulation. Their main role is in cell-signaling, and, because of their hydrophobic nature, their main actions are limited to paracrine (cell-to-cell) or autocrine (same cell) signaling, rather than systemic effects. Unique characteristics of the EC system include (*i*) the lipid structure of the endocannabinoids, formed from the internal lipid constituents of cellular membrane, making them hydrophobic with limited mobility in an aqueous environment, (*ii*) their synthesis 'on demand' (no storage) with a very short half-life, (*iii*) the local cell-signaling action (paracrine or autocrine), (*iv*) the retrograde transmission in the brain; travels backward from postsynaptic to presynaptic cells, (*v*) the presence of two distinct G-protein–coupled

Table 2
Cannabinoid-based therapies to treat pain and depression.

Condition	Cannabinoid-based drug	Outcomes for pain	Outcomes for depression and anxiety
HIV	Marijuana	↓Muscle, nerve pain	↓Anxiety
Cancer	Nabilone	↓Pain score	↓Overall stress
Fibromyalgia	Nabilone	↓Pain	↓Anxiety
Psychiatric disorders	Nabilone	↓Pain	↓Post-traumatic stress disorder symptoms
Chronic central neuropathic pain	Δ^9-THC	↓Pain and pain intensity	↓Anxiety
Diabetic peripheral neuropathy	Sativex (Δ^9-THC, cannabidiol)	↓Pain	↑Quality of life

receptors in brain (CB1R) and immune system (CB2R), and (*vi*) the regulation of the EC system bioactivity through degradation of endocannabinoids by FAAH.

With scientific evidence suggesting their role in inflammation, insulin sensitivity, and fat and energy metabolism, it has been suggested that inhibition of endocannabinoids [26] or augmenting EC signaling by local application of ECs [34] may be effective approaches for reducing the prevalence of the metabolic syndrome and augmenting the benefits of physical exercise. Furthermore, modulation of the EC system may be a cure for more chronic neurologic and immune conditions. Research in animal models suggests the possible use of cannabinoids as anticancer drugs [32,37,38]. Many questions are left unanswered about this relatively newly discovered regulatory system. Further investigation into this exciting field promises to shed insights into the mechanisms of health and disease and provide new therapeutic options.

8. Conclusion

In summary, the EC system is a unique and ubiquitous cell-signaling system that is just beginning to be understood. The biochemistry of EC synthesis, metabolism, and bioactivity has been difficult to study in the past. Newer techniques such as genetically modified animals, pharmacologic probes, and molecular biological tools promise to reveal some of these mysteries in the near future. The greater promise is that with this understanding, the EC system will yield an important therapeutic target for future pharmacologic therapy. Keeping in mind the potential pitfalls of ubiquitously activating this delicately balanced signaling network, with measured approaches- like targeted, tissue-specific delivery, we are not far away from unravelling the previously unexplored benefits of this elixir.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.plefa.2018.11.016.

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